INTRINSIC DISORDER, SCAFFOLDS, AND STOCHASTIC MACHINES

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Abstract

Scaffold proteins bind additional proteins that then carry out multi-step pathways. How do such machines work? Here a new hypothesis is proposed for the complex consisting of axin, two kinases – GSK3β and CK1α, and β-catenin. The pathway involves four discrete phosphorylations of β-catenin by the two kinases. Like many other scaffold proteins, axin is mostly unstructured [1, 2]. With a length of about 800 residues, axin forms two small domains of less than 100 residues each, and uses only a small number of residues, about 20 per interaction, to bind to GSK3β and β-catenin [1], and presumably also to bind to CK1α. Thus, even with the two domains and 3 partners, axin remains mostly unfolded. The hypothesis is that the unstructured axin molecule holds the three globular proteins in very high local concentrations, like three globules on a rope, and that, by random motions, first CK1α and then GSK3β phosphorylate the disordered tail of β-catenin successively four times. The "conformational changes" of axin that lead to acceleration of phosphorylation are neither specific nor coordinated, but rather are entirely stochastic, with stereochemical fit between the enzymes and their targets leading to the correct ordering of the four phosphorylation steps. In this hypothesis, the scaffold protein acts simply as a flexible tether that leads to acceleration of the multiple steps in the pathway by raising the local concentrations of the key components and by allowing the various components the freedom to collide in various orientations until productive collisions result. Thus, the steps of the pathway are carried out by a stochastic machine. This may be a general mechanism for scaffold-based molecular machines.

References

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